Exhibit A

Preparation of Enteric-Coated Microcapsules for Tableting by Spray-Drying Technique and *In Vitro* Simulation of Drug Release from the Tablet in GI Tract

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Abstract □ Improved methods were developed for the preparation of enteric-coated microcapsules for tableting by a spray-drying technique, and the drug release behavior from the tableted microcapsules was investigated using a disintegration apparatus and a new *in vitro* method of simulating the GI tract. As a model system, ammonium solutions of sulfamethoxazole and cellulose acetate phthalate were spray dried using a centrifugal wheel atomizer at 140°. Additives such as colloidal silica, montmorillonite clay, and talc were included in the formulations for spray drying. The influence of the additives on the particle diameter, density, packing properties, and compressibility of the product and on the release characteristics of the resultant tablet *in vitro* were investigated. The additives in the formulations greatly improved the flow properties of the spray-dried products, which could be tableted easily. Products from the nonadditive formulations could not be tableted due to their poor flowability. The hardness and disintegration rate of the tablet increased with increasing concentration of additives in the formulations. X-ray analysis and IR spectroscopy confirmed that the crystals of sulfamethoxazole in the spray-dried microcapsules with cellulose acetate phthalate were converted from Form I to Form II. *In vitro* release characteristics of the tablets were studied using a disintegrator (JP) in buffer solutions (pH 1.2 and 7.5) and distilled water. Enteric action of the spray-dried products was proved by comparison with the original nontreated powders. The additives in the tablet increased the release rate at the initial stage in all dissolution media used. A new *in vitro* release simulator was devised consisting of a flow-type dissolution container in which the pH of the medium was changed continuously from 1.2 to 7.0 to simulate the pH change of tablets exposed to the GI tract.

Keyphrases □ Microcapsules—preparation of enteric-coated microcapsules for tableting by a spray-drying technique, drug release from tableted microcapsules □ Tablets—preparation of enteric-coated microcapsules for tableting, drug release from tableted microcapsules □ Dissolution—tableted enteric-coated microcapsules

Spray-drying techniques have been used widely for drying heat-sensitive foods, pharmaceuticals, and other substances because of the rapid evaporation of the solvent from the droplets. Interest has been renewed in this technique for the preparation of agglomerates or microcapsules of pharmaceuticals. Speiser *et al.* (1) prepared microcapsules of barbituric acid employing a spray polycondensation method. Kawashima and Takenaka (2) produced sustained-action antacid tablets by compressing spray-dried microcapsules of magnesium carbonate. The successful results from these studies encouraged further development of this technique for preparation of a new dosage form.

One objective of the present study was to prepare enteric-coated microcapsules of sulfamethoxazole efficiently by a spray-drying technique instead of by a phase separation method (3). Proper formulation and spray-drying conditions were sought for producing microcapsules with enteric action that meet the requirement for tableting. Another objective was to devise a new *in vitro* simulator for the GI tract to evaluate the enteric action of the tablet prepared by compressing the spray-dried products.

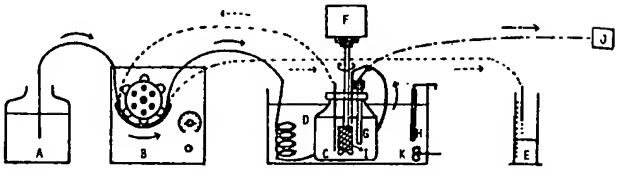

Figure 1—*Apparatus for a new* in vitro *release simulator. Key: A, alkaline solution supplier; B, roller pump (1.27 ml/min); C, modified dissolution apparatus; D, water bath (37°); E, receiving reservoir; F, motor (94 rpm); G, pH electrode; H, heater; I, USP basket modified by attaching four-blade propeller; J, pH meter; K, stirrer; and — and ---, polyethylene tube plugged with cotton at initial points.*

EXPERIMENTAL

Spray-Drying Technique—Sulfamethoxazole[1] was used as received as a model pharmaceutical for microencapsulation or agglomeration. Sulfamethoxazole and cellulose acetate phthalate[2] (50 g each) were dissolved in 1 liter of 5% NH_4OH. To this solution were added 0, 30, and 50 g of colloidal silica[3], montmorillonite clay[4], and talc[5]. Formulations without cellulose acetate phthalate also were prepared as a reference for testing the enteric action.

The slurries or solutions were atomized into a drying chamber by a centrifugal wheel atomizer at 40,000 rpm. The drying chamber was maintained at 140 ± 10°. The dried products were collected by a cyclone collector.

Measurement of Physicochemical Properties—The particle size of the spray-dried products was measured by a photographic counting method using a particle-size analyzer[6]. Packing properties and particle density were measured by a tapping powder method and with a helium–air comparison pycnometer[7], respectively. The surface topography of the spray-dried particles coated with gold was investigated with a scanning electron microscope[8]. To analyze the crystalline form of sulfamethoxazole in the spray-dried products, X-ray diffraction patterns[9] and IR spectra[10] were obtained.

Dissolution Test of Tablets Prepared from Spray-Dried Products—Spray-dried products with additives and the mixtures with microcrystalline cellulose[11] (1:1) were tableted using a single-punch tablet machine. The dimensions and weights of 10 tablets were measured. The hardness of the tablets was measured by a moving platen-type hardness tester[12]. Tablet hardness is presented as average values.

The dissolution test of a tablet was undertaken using the JP IX disintegration apparatus and the specified disintegration test solutions (pH 1.2 and 7.5) and distilled water at 37°. Tests also were conducted with a new *in vitro* release simulator (Fig. 1) with a flow-type dissolution container in which the pH of the medium was changed continuously to simulate the pH change on the surface of the tablets exposed in the GI tract.

[1] Shionogi Pharmaceutical Co., Japan.
[2] Kishida Chemical Co., Japan.
[3] Japan Aerosil K.K., Japan.
[4] Veegum-K, R. T. Vanderbilt Co.
[5] Matsumura Sangyo Co., Japan.
[6] Karl Zeiss TGZ-3.
[7] Model 1302, Micromeritics Instrument Co.
[8] Nihon Denshi JMS-S1.
[9] Nihon Denshi JDX.
[10] Nihon Denshi DS-403G.
[11] Asahi Kasei Kogyo K.K., Japan.
[12] Kyowa Seiko K.K., Japan.

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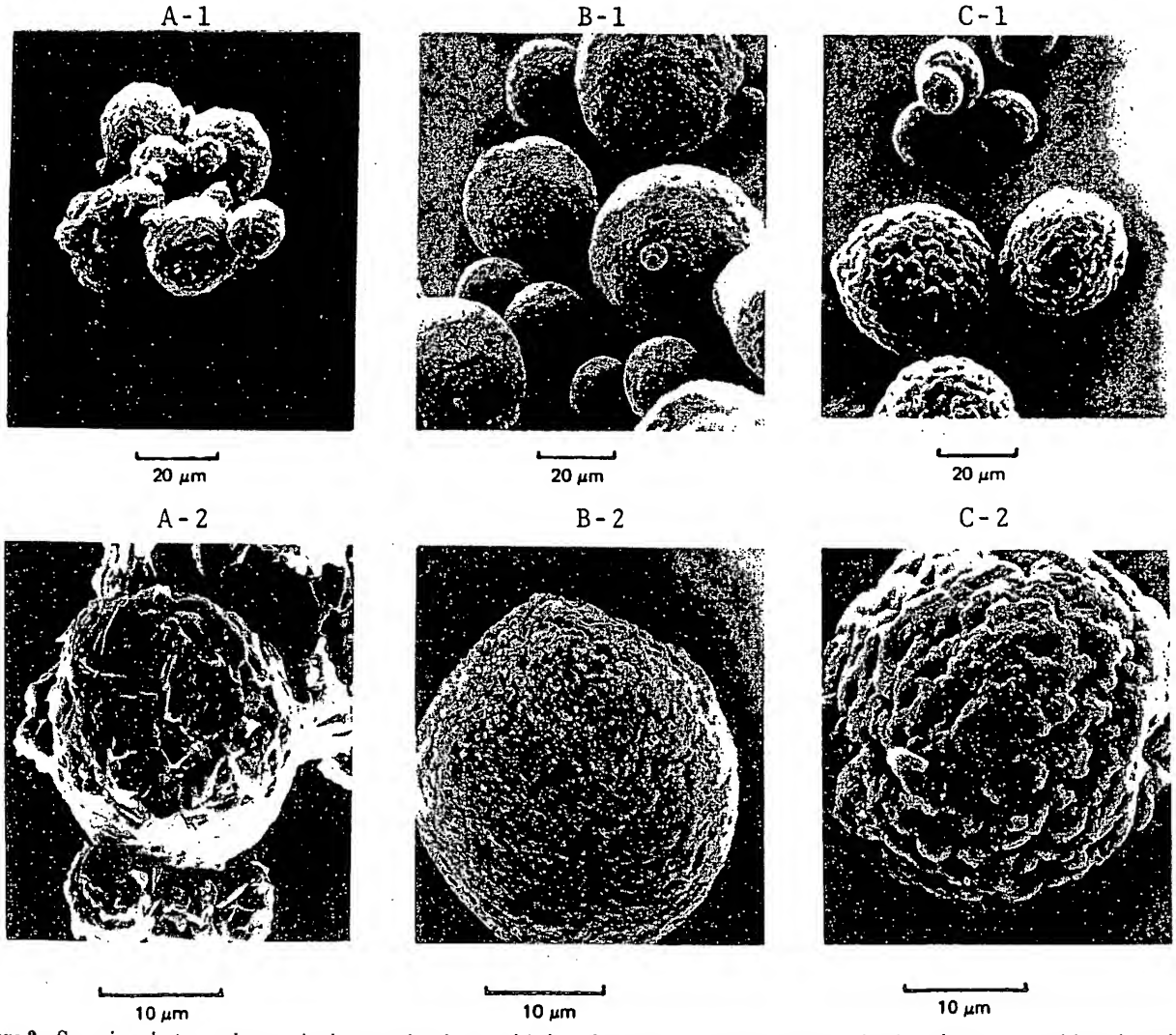
'able I—Micromeritic Properties of Powdered and Tableted Spray-Dried Products [a]

Property	Montmorillonite Clay		Colloidal Silica		Talc		No Additive
			With Cellulose Acetate Phthalate				
/eight of additive, g	30	50	30	50	30	50	—
$_{av}$, μm	8.8	12.8	12.8	15.9	13.4	9.9	22.2
$_{w}$, cm^2/g	4947	3386	3190	2498	2986	4126	2159
, g/cm^3	1.38	1.39	1.50	1.50	1.50	1.50	1.25
	0.29	0.32	0.14	0.06	0.36	0.31	0.37
	0.05	0.08	0.07	0.12	0.05	0.05	0.07
	0.12	0.05	0.07	0.07	0.19	0.16	—
', kg	3.7	24.2	2.2	12.4	1.1	2.3	—
			Without Cellulose Acetate Phthalate				
/eight of additive, g	30		30	50	30	50	
$_{av}$, μm	8.1		7.1	3.6	3.5	8.8	
$_{w}$, cm^2/g	4619		5093	9898	10,988	3940	
, g/cm^3	1.61		1.66	1.68	1.55	1.72	
	0.31		0.13	0.16	0.39	0.45	
	0.06		0.13	0.07	0.07	0.09	
	0.21		0.63	0.45	0.31	0.32	
, kg	8.7		45	—	2.27	3.77	

[a] Key: D_{av}, geometric mean diameter; S_w, specific area measured by air permeability method; ρ, porosity of tablet; and H, hardness of tablet.



gure 2—*Scanning electron microscopic photographs of spray-dried products. Key: A-1 and A-2, spray-dried products prepared from formulations ntaining cellulose acetate phthalate (50 g); B-1 and B-2, spray-dried products prepared from formulations containing cellulose acetate phthalate 0 g) and colloidal silica (50 g); and C-1 and C-2, spray-dried products prepared from formulations containing colloidal silica (50 g).*

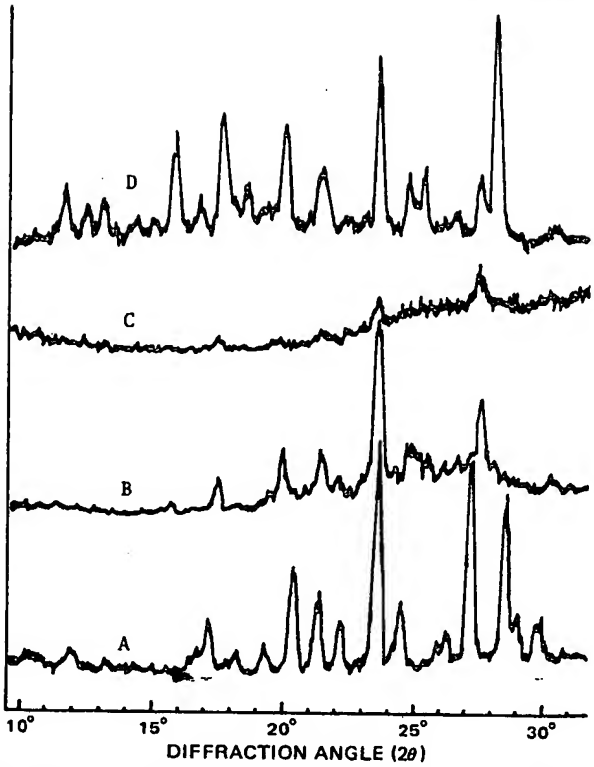


Figure 3—*X-ray diffraction patterns of original and spray-dried sulfamethoxazole. Key: A, Form I, original sulfamethoxazole; B, Form II, sulfamethoxazole recrystallized in water at dry ice–acetone temperature; C, spray-dried products prepared from formulations containing cellulose acetate phthalate (50 g) and colloidal silica (50 g); and D, spray-dried products prepared from formulations containing talc (50 g).*

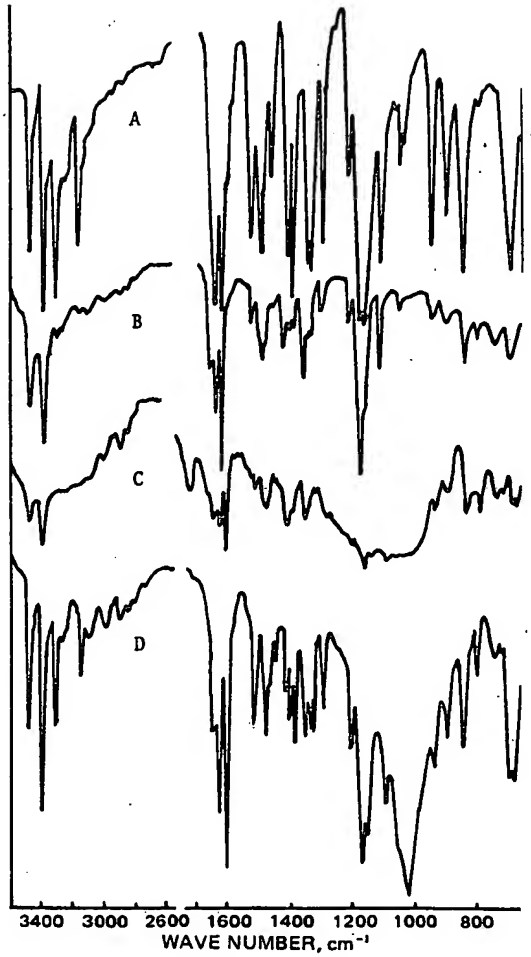


Figure 4—*IR spectra of original and spray-dried sulfamethoxazole Key: A, Form I, original sulfamethoxazole; B, Form II, sulfamethoxazole recrystallized in water at dry ice–acetone temperature; C, spray-dried products prepared from formulations containing cellulose acetate phthalate (50 g) and colloidal silica (50 g); and D, spray-dried products prepared from formulations containing talc (50 g).*

The test was carried out by placing a tablet in the basket specified in the USP dissolution apparatus, which was modified by attaching a four-blade propeller. This basket was set 1.0 ± 0.2 cm from the bottom of the container and was rotated at 94 rpm. The pH 1.2 medium (300 ml) was introduced into the dissolution apparatus, followed by the addition of the alkaline medium (pH 7.5) at a rate of 1.27 ml/min. Simultaneously, the agitated dissolution medium was removed at the same rate to a reservoir using a rotating-type pump[13]. With this technique, the volume of medium in the container was held to 300 ml and the pH of the medium was changed continuously from 1.2 to 7.0. This pH change corresponds to that of the GI tract. The pH change in the dissolution medium was monitored by a pH meter placed in the dissolution medium.

Aliquots of 2 ml of the dissolution medium in the apparatus and the reservoir were sampled at prescribed intervals through a pipet plugged with cotton and were filtered through a Millipore filter (0.3 μm). Aliquots of distilled water (same volume and temperature) were added immediately to the dissolution apparatus to keep the volume of the dissolution medium in the container constant during the test. The concentration of dissolved sulfamethoxazole in the medium was determined spectrophotometrically at a suitable UV region using a double-beam spectrophotometer[14].

RESULTS AND DISCUSSION

Physicochemical Properties of Spray-Dried Products—The size distribution of the spray-dried particles was described in log-normal form. The geometric mean diameter ranged from 3.6 to 22.0 μm. The formulations including cellulose acetate phthalate and the additives yielded smaller products than the formulations without the additives. The products prepared from the formulations with the additives alone became smaller compared to the others (Table I).

Scanning electron microscopic photographs of the spray-dried products are shown in Fig. 2. The surfaces of the products prepared from the nonadditive formulations were covered with flake-like crusts (Fig. 2A). When the additives were added to the formulations, no flakes appeared, and the surface had an orange peel texture (Fig. 2B). Figure 2C shows an

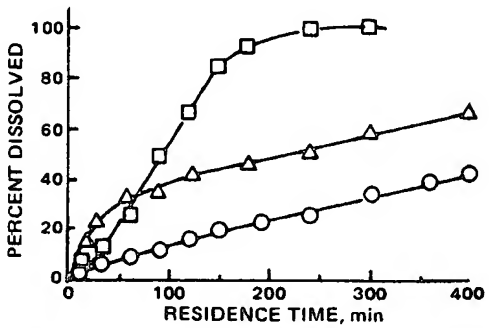


Figure 5—*Release patterns of tablets without microcrystalline cellulose in various media. Key: ○, distilled water; △, pH 1.2; and □, pH 7.5. The additive was 30 g of colloidal silica.*

[13] Furue Science Co., Japan.
[14] Hitachi model 556.

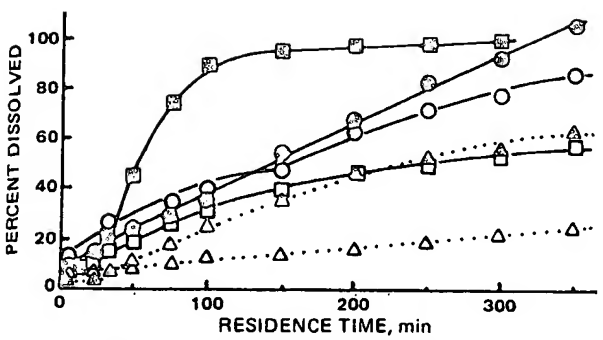


Figure 6—*Drug release patterns of tablets without cellulose acetate phthalate and microcrystalline cellulose and with varying amounts of colloidal silica in various dissolution media. Key: ○, 30 g, pH 1.2 medium; ○, 50 g, pH 1.2 medium; □, 30 g, pH 7.5 medium; □, 50 g, pH 7.5 medium; △, 30 g, distilled water; and △, 50 g, distilled water.*

image of the product with the additives alone, which seems to be an agglomerate composed of lobes. Many sulfamethoxazole crystals apparently are adsorbed onto the surface.

The characteristic bulkiness of the spray-dried product from the formulations with cellulose acetate phthalate alone (Fig. 2A) suggests that their particle density and packing property differ from those of the other formulations. It was assumed that these products might be lighter than those with the additives. This assumption was proved by the particle density data given in Table I. The products including the additives alone had a higher particle density. The packing process of the spray-dried products in a tapped graduated cylinder was represented by (4):

$$n/c = 1/ab + n/a \quad \text{(Eq. 1)}$$

$$c = (V_0 - V_n)/V_n \quad \text{(Eq. 2)}$$

where b is a constant, n is the number of taps, V_0 is the volume of powder in a measuring cylinder at the loosest packing, and V_n is the volume after the nth tapping. The parameter a in Eq. 1 for the products without additives was found to be larger than that of the particles with montmorillonite clay and colloidal silica. This finding indicates that the particles with the additives might be packed more easily since a corresponds to the proportion of consolidation at the closest packing attained.

Tablets could not be made directly by compressing the products without the additives due to their poor flowabilities. The products including the additives were tableted easily. Compressibility of the

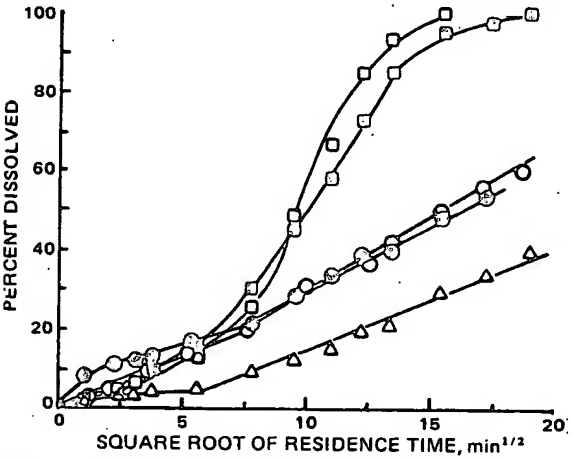


Figure 7—*Percentage of drug release as a function of the square root of the residence time with and without cellulose acetate phthalate, without microcrystalline cellulose, and with varying amounts of colloidal silica in various dissolution media. Key for formulations with cellulose acetate phthalate: ◎, 50 g, pH 1.2 medium; □, 30 g, pH 7.5 medium; ▣, 50 g, pH 7.5 medium; and △, 30 g, distilled water; ○ represents a formulation without cellulose-acetate phthalate and containing 50 g of colloidal silica in a pH 7.5 medium.*

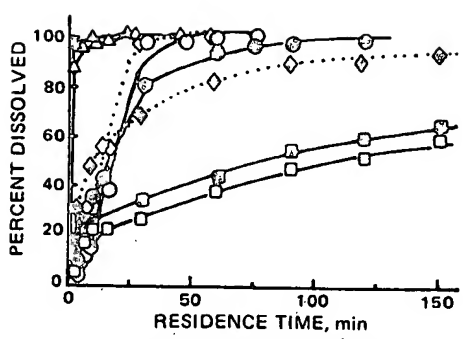


Figure 8—*Drug release patterns of tablets containing microcrystalline cellulose with varying amounts of colloidal silica in various dissolution media. Key: □, 0 g, pH 1.2 medium; □, 30 g, pH 1.2 medium; ○, 0 g, pH 7.5 medium; ○, 30 g, pH 7.5 medium; ◇, 0 g, distilled water; and ◇, 30 g, distilled water. The original powder also was dissolved in pH 1.2 (△) and 7.5 (△) media.*

spray-dried products including the additives was improved with increasing amounts of the additives, as indicated by their greater hardness and smaller porosity. This trend clearly appeared with the tablets containing colloidal silica and montmorillonite clay (Table I).

The crystalline forms of the spray-dried products were investigated by X-ray diffraction analysis and IR spectroscopy. The IR spectra and X-ray diffraction patterns of the untreated original sulfamethoxazole used in the present study identified the crystals as Form I, as defined previously (5). The peaks in the X-ray diffraction patterns of the spray-dried products were less intense than those of the original crystals (Fig. 3). This finding indicated that some sulfamethoxazole crystals were converted to a disordered form due to rapid crystallization.

In the patterns of the products with cellulose acetate phthalate, regardless of whether the additives were included, fairly characteristic peaks of Form II appeared. Form II was prepared as a reference by recrystallization in water at dry ice–acetone temperature (Fig. 3). The X-ray diffraction patterns of the products with colloidal silica and montmorillonite clay proved that they were Form I. The patterns of the products with talc exhibited peaks of both Forms I and II, indicating that they were a mixture.

The polymorphic forms of the spray-dried products also were confirmed by their IR spectra (Fig. 4). The spray-dried products with cellulose acetate phthalate exhibited the characteristic bands of Form II at 3080, 2990, and 1640 cm^{-1}, which did not appear in the spectrum of Form I. Differences in the spectra from Form I also were found at 1395, 1330, 1150, and 750 cm^{-1}. When cellulose acetate phthalate was excluded from the formulations, the spectra of the spray-dried products changed to those of Form I. Spectra of the products with talc exhibited the intense bands at 3300 and 3150 cm^{-1} and several characteristic bands of Form II. This result suggests that the products with talc contain Forms I and II.

It has been suggested that polymorphism in sulfonamides may be

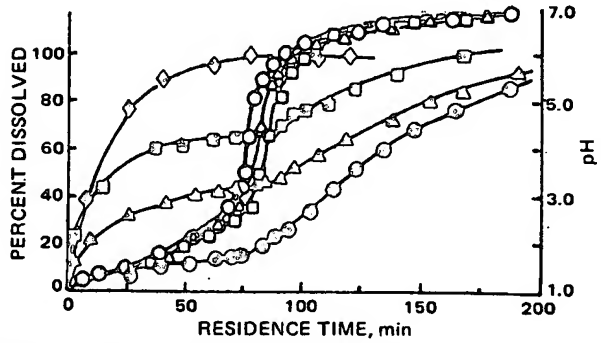


Figure 9—*Drug release (closed symbols) and pH change (open symbols) patterns in a flow-type simulator for formulations containing varying amounts of colloidal silica. Key for formulations containing cellulose acetate phthalate: ◎, ○, 0 g; ▲, △, 30 g; and ▣, □, 50 g. The formulation without cellulose acetate phthalate and containing 50 g of colloidal silica is represented by ◆.*

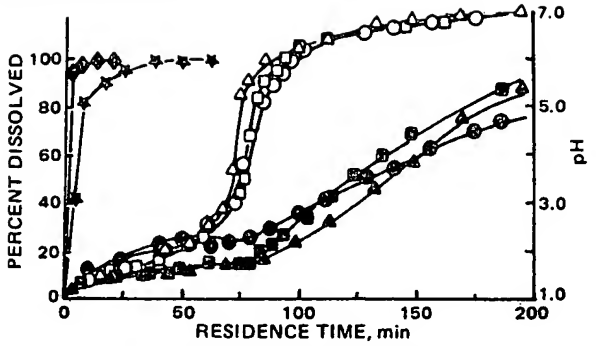


Figure 10—*Drug release (closed symbols) and pH change (open symbols) patterns in a flow-type simulator for formulations containing varying amounts of additives. Key for formulations with cellulose acetate phthalate: ●, ○, 50 g of talc; ▲, △, 50 g of montmorillonite clay; and ■, □, no additive. Key for formulations without cellulose acetate phthalate: ★, ☆, 30 g of talc; and ♦, ◇, 30 g of montmorillonite clay.*

rought about due to the intermolecular hydrogen bonding (6, 7). Hydrogen bonding in the alkaline solutions used might be attained mainly y the interaction between the hydrogen of the *p*-amino group and the xygen of the S–O group in the sulfamethoxazole molecule. Furthermore, ellulose acetate phthalate molecules might influence the way in which ie sulfamethoxazole molecules associate in the solution. This effect was onfirmed by the fact that the products from the simple formulations ithout cellulose acetate phthalate or the additives exhibited Form I but ot Form II. Such a polymorphism might make the drug metastable, but could improve solubility.

Dissolution Behavior of Tablets in Disintegration Apparatus—issolution patterns of the tablets of the spray-dried products with colidal silica and cellulose acetate phthalate in the disintegration test olutions (pH 1.2 and 7.5) and distilled water were determined using a isintegration apparatus (Fig. 5). The dissolution curves in the alkaline olution were distinguished by their much faster release rate from those i the other media used due to the enteric-coating action of the cellulose etate phthalate contained in the tablet. Although the initial release rate i the acidic solution was faster than in distilled water, the slope of the lease curve became almost identical at the later stage. In the alkaline olution, the tablets were gradually disintegrated to fine particles and few small pieces; in the acidic media, disintegration did not occur, and nly the size of the tablet slowly decreased during the dissolution proess.

The dissolution behavior of the tablets prepared from the formulations ith colloidal silica but without cellulose acetate phthalate is shown in ig. 6. There was less variation in the rate in the three dissolution media ed. The colloidal silica may have acted as a disintegrating agent due o its wettability, which might have resulted in an increased release rate. owever, when the concentration of colloidal silica in the tablet was inreased, the release rate was decreased significantly, which might have en due to a matrix-like structure of the tablet binding strongly with olloidal silica.

These differences in the release behavior of the tablets were explained y plotting the data on a semisquare root graph (Fig. 7). In the acidic olution and distilled water, all release patterns of the tablets, regardless the formulation, became fairly straight lines after enhanced dissolution eriods. This finding indicates that the release process at the later stage eys the Higuchi model (8) represented by:

$$Q = [D(2A - C_s)C_s t]^{1/2} \quad \text{(Eq. 3)}$$

here Q is the amount dissolved per unit area of exposure at time t, A the total amount of drug present in the matrix per unit volume, C_s is ie solubility of the drug in the external phase of the matrix, and D is the iffusion constant. When $C_s \ll A$, Eq. 3 can be transformed to a more nvenient form to exhibit the release patterns described in Fig. 7 (9):

$$C_r = 100[S_v(2DC_s t/A)^{1/2}] \quad \text{(Eq. 4)}$$

here C_r is the percent of the drug dissolved and S_v is the specific surface ea. In alkaline solution, the release patterns of the tablets with and ithout cellulose acetate phthalate exhibited sigmoid curves and straight ies, respectively.

When microcrystalline celluloses were mixed into the spray-dried products in a 1:1 ratio, tablets could be made even if the products without the additives were used. However, the hardness of the tablet was insufficient for practical use compared with the tablets containing the additives. The dissolution rate of the tablets containing microcrystalline cellulose became faster than that of the tablets without it in all dissolution media due to their rapid disintegration. The distinct discrepancies of the release patterns depended on the type of dissolution medium used (Fig. 8). The prolonged release in the acidic medium was clearly evident when compared to the mixtures of microcrystalline cellulose and original sulfamethoxazole. Thus, the effectiveness of the enteric coating of the spray-dried products containing cellulose acetate phthalate is proved in Figs. 7 and 8.

In the alkaline medium and in distilled water, the dissolution rate was delayed when the additives were included in the formulations. In the acidic solution, the release rate of the tablet with the additives was faster than for those without them. This result might have been due to the fact that the additives included in the discrete microcapsules could promote penetration of the solvent.

Dissolution Behavior of Tablet Containing Various Additives in a Flow-Type Simulator—Gastric contents do not become alkaline merely as a result of passing through the pylorus. The upper small intestine is more likely to be slightly acidic. Thus, to simulate *in vivo* action, it may be desirable to conduct the enteric test in a dissolution medium whose pH is changed continuously from 1.2 to 7.0 rather than in a medium fixed at pH 7.0 or above. Release patterns of tablets prepared from the mixtures of microcrystalline cellulose and the spray-dried products containing various additives exposed to a medium whose pH changed continuously from 1.2 to 7.0 are shown in Figs. 9 and 10. The pH change of the medium with residence time followed a sigmoid curve which varied slightly from batch to batch, although the patterns were almost identical.

The release rate of the tablets with cellulose acetate phthalate was relatively fast at the initial stage, followed by a stage with a decreased rate. After the residence time of 70–90 min at pH 3.5–5.5, the release rate increased rapidly again, which caused an inflection on the release curve. It is reasonable to assume that this point corresponds to the starting point of the enteric action. By increasing the concentration of colloidal silica, the release rate at the initial stage (pH values of <3.5–4.0) increased due to enhancement of the solvent penetrating action by colloidal silica (Fig. 9).

The release patterns of the tablets without cellulose acetate phthalate were characterized by a smooth convex curve without an inflection point. With talc and montmorillonite clay, similar enteric action of the tablets containing cellulose acetate phthalate was observed; however, some solvent penetration appeared at the lower concentrations of these additives. At the later stage (pH > 5.0), the release rate was more delayed compared to that of the additive-free tablets. This result might have been due to the fact that the drug was adsorbed firmly in the pores of the additives, forming a matrix-like structure.

From these results, it is concluded that the enteric-coating behavior of the tablets was more clearly demonstrated by using the flow-type simulator and a medium whose pH changed continuously than by studying dissolution and disintegration at constant pH values. By this technique, it also was possible to detect the pH above which the enteric action was overcome.

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Simple Rapid Method for the Preparation of Enteric-Coated Microspheres

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Abstract □ A method is presented for encapsulating high molecular weight biological materials such as viral antigen, concanavalin A, and other proteins with cellulose acetate phthalate. The method is simple, inexpensive, and rapid; the process takes ~15 min. Capsules generated by this method are produced as microspheres 1–3 mm in diameter. They are stable for at least 6 h in simulated gastric conditions, but disintegrate rapidly under simulated intestinal conditions. Encapsulation had no effect on the activity of the biological materials. The method has potentially wide application for encapsulation of drugs and other substances.

Keyphrases □ Microspheres—enteric-coated, method for rapid preparation, encapsulation, cellulose acetate phthalate □ Encapsulation—method for the rapid preparation of enteric-coated microspheres, cellulose acetate phthalate □ Cellulose acetate phthalate—method for the preparation of enteric-coated microspheres, encapsulation □ Delivery systems—enteric-coated microspheres, cellulose acetate phthalate, method for rapid preparation

Cellulose acetate phthalate (I) has been used extensively as an enteric coating. Due to the presence of ionizable phthalate groups, the polymer is insoluble in acid media ≤pH 5, but is soluble when the pH is ≥6 (1). Since it is also remarkably inert *in vivo* (2), it is used to coat material for the release of drugs and other substances in the intestine. In recent years, I-coating technologies have been applied to the encapsulation of many biologically active materials, ranging from low molecular weight drugs [*e.g.*, sodium salicylate and phenacetin (3, 4)] to microorganisms [*e.g.*, viruses and bacteria (5–7)].

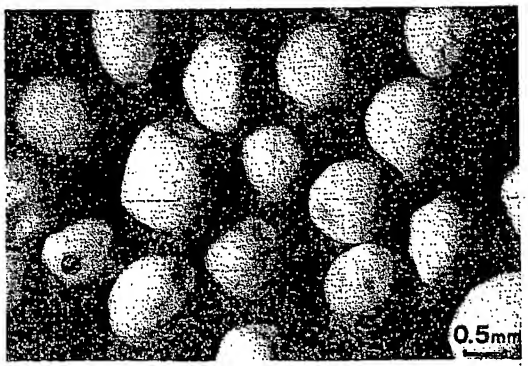

Figure 1—*Sucrose microspheres prepared as detailed in the text (formation time: 5 min).*

This report describes the development of an enteric coating for an oral vaccine used to protect wildlife against rabies. Studies on the vaccine itself will be reported elsewhere. The present report describes the principles of a method for encapsulation of the vaccine in the form of quasi-spherical particles ~1–3 mm in diameter (microspheres). The method is simple, rapid, and can be used to encapsulate a wide variety of materials. Therefore it has potential applications other than vaccine encapsulation.

EXPERIMENTAL

Materials—Core materials (*i.e.*, high molecular weight materials) that were encapsulated included rabies antigen (ERA-H strain of virus grown in BHK-21 cells and inactivated with β-propiolactone[1]), concanavalin A[1], and bovine serum albumin[1]. Radiolabeling of these materials with iodine-125 was carried out essentially as described by Thorell and Larson (8). Before use, the labeled preparations were passed through columns of Sephadex G-25[2] and extensively dialyzed against phosphate-buffered

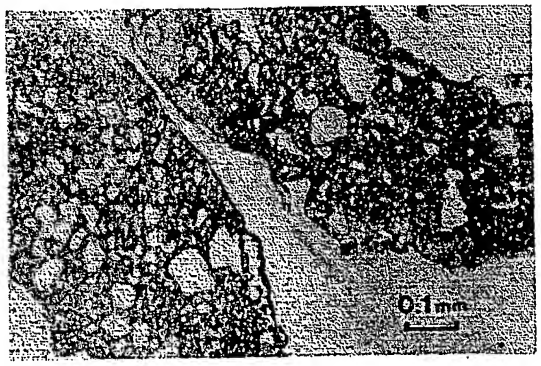

Figure 2—*Paraffin section (hematoxylin–eosin stain) of part of two sucrose microspheres showing the I matrix and the randomly distributed pockets that contained microparticles of the sucrose/core material. Hollow interiors of the microspheres are at the top right and bottom left of the photomicrograph.*

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Pharmacia, Uppsala, Sweden.

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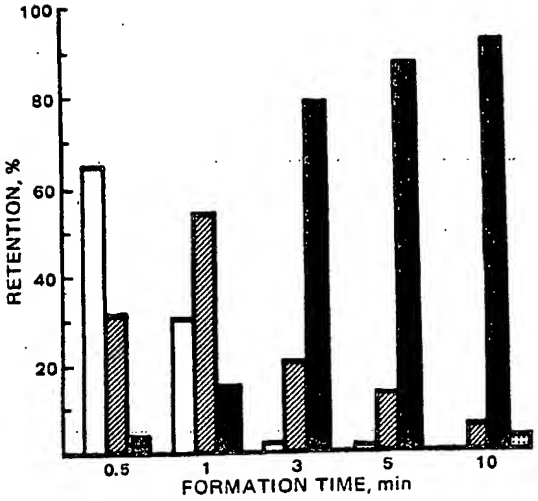

Figure 3—*Influence of formation time on the size of the microspheres. Formation was terminated by the addition of chloroform. Formed microspheres were collected, dried in air, and graded by passage through a series of U.S. standard stainless steel sieves mounted on a portable sieve shaker[9], before being weighed. Key: (□) No. 50 sieve; (▨) No. 20 sieve; (■) No. 16 sieve; (▩) No. 12 sieve.*

saline to remove any free iodine. In the final preparations, >99% of the radioactivity was associated with trichloroacetic acid-precipitable (*i.e.*, high molecular weight) material.

Two lots of cellulose acetate phthalate[3] (A and B) were employed as the encapsulation material. Lot A had been stored for several years and had a pungent smell of acetic acid. Lot B was newly purchased and was practically odorless. Although both preparations were acceptable, they required slightly different conditions for optimal formation of microspheres.

Formation of Microspheres—The core material (maximum 50 mg) was suspended in 200 mL of 5% sucrose (w/v), shell-frozen, and then freeze-dried. The resulting powder was then triturated in a 1:4 ratio with finely divided sucrose containing up to 5% cornstarch and pressed through a No. 50 U.S. stainless steel sieve. This powder was then suspended in 200 mL of white paraffin oil[4] contained in a 400-mL beaker. The mixture

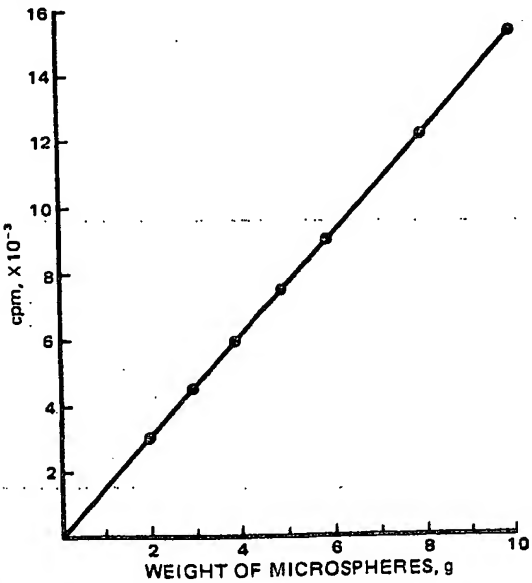

Figure 4—*Relationship between weight and core material content of the microspheres. Core material was [^{125}I]viral antigen, measured by radioactivity.*

[3] Lots #193(A) and #A9E(B); Eastman Kodak, Rochester, N.Y.
[4] Anachemia Chemicals Ltd., Mississauga, Ont.

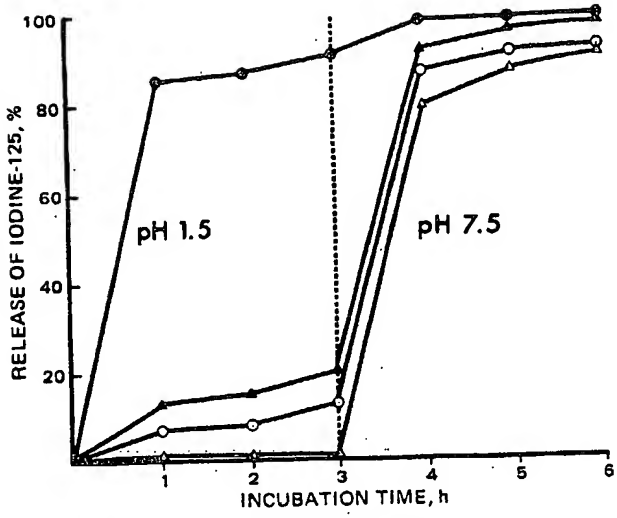

Figure 5—*Influence of pH of the incubation medium on the release of encapsulated viral radiolabel at 37°C. Key: (●) uncoated; (▲) I coated; (○) I–diethyl phthalate coated; (△) I–diethyl phthalate–wax coated.*

was dispersed by stirring at ~260 rpm with a 44-mm polyethylene three-blade paddle fitted to a high-torque stirrer[5]. To the suspension was added 20 mL of 10% (w/v) I in acetone–95% ethanol (9:1). Stirring was continued for 5 min to allow the microspheres to form, and then 75 mL of chloroform was added. The suspending medium was then decanted, and the microspheres were briefly resuspended in 75 mL of chloroform and air-dried at ambient temperature.

With one lot of I (B), some clumping of the microspheres was observed when they were removed from the chloroform. This was circumvented by stirring the suspension for 10–15 min after addition of the first volume of chloroform, prior to decanting.

In some preparations, the plasticizer diethyl phthalate[6] was included since it has been shown to increase the pliability and reduce the amount of moisture absorbed by I-coated capsules (9). The plasticizer (3% w/v) was dissolved in the I solution before addition to the encapsulation medium.

To further reduce the permeability of the microspheres, a wax coating was applied. Carnauba wax (1 g) was dissolved in 200 mL of white paraffin oil at 70°C and cooled to <45°C. The formed microspheres were then suspended in this for 15 min, with constant stirring. The wax solution was then decanted, and the microspheres were collected on filter paper to absorb the excess wax solution.

Release of Core Material—Stability of the microspheres was studied under conditions simulating those of the stomach and intestine. Breakdown or dissolution of the particles was monitored by measuring the release of iodine-125 and sucrose into the supernatant medium.

In most experiments, 2.5-g aliquots of the microsphere preparations were suspended in 20 mL of simulated gastric juice USP, without pepsin (*i.e.*, 0.08 M HCl containing 0.2% NaCl, pH 1.2). The suspension was incubated for 3 h at 37°C, with constant shaking at 160 rpm, on a clinical rotator[7]. At the end of each 1-h period, 1.0 mL of supernatant was removed, clarified by low-speed centrifugation (~7000×*g* for 10 min), and assayed for the presence of released encapsulated materials. Immediately following the 3-h incubation period, the simulated gastric medium was aspirated off, and the remaining microspheres were rinsed briefly with 5 mL of warm distilled water which was then discarded. The particles were incubated for a further 3 h at 37°C with 20 mL of simulated intestinal juice USP, without pancreatin (*i.e.*, 0.05 M KH_2PO_4 adjusted to pH 7.5 with 0.04 M NaOH). The hourly sampling process was repeated as before. The pH of the suspension was monitored by the addition of a few drops of 0.001%-phenol red and adjusted when necessary with small volumes of alkali (usually 75 μL of 10 M NaOH after 1 and 2 h).

Assays—Levels of iodine-125 in the supernatant were measured by direct counting in a gamma-radiation counter[8]. Sucrose was measured by the anthrone reaction (10). There was no significant interference in this colorimetric reaction by dissolved I at the dilutions used.

[5] Type RZR1, "Caframo", Wiarton, Ont.
[6] BDH Chemicals, Toronto, Ont.
[7] Fisher Scientific Co., Fair Lawn, N.J.
[8] Gammacord; Ames Co., Elkhart, Ind.

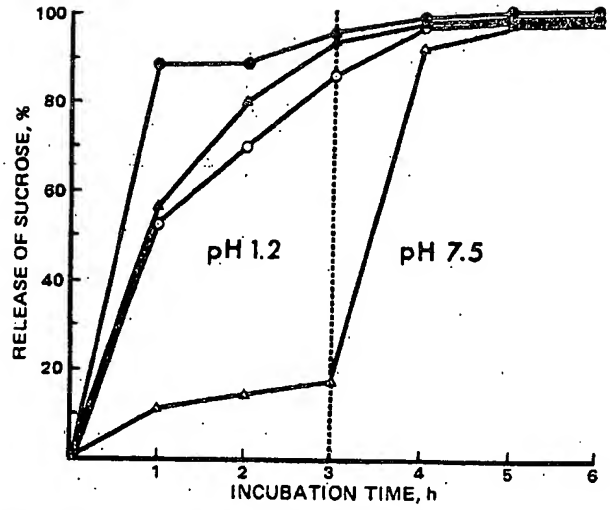

Figure 6—*Influence of pH of the incubation medium on the release of encapsulated sucrose at 37°C. Symbols are the same as in Fig. 5.*

Before encapsulation, >99% of the iodine-125 activity was associated with trichloroacetic acid-precipitable material. To determine if any degradation or dissociation had occurred during the encapsulation and/or release studies, the hourly samples were adjusted to 10% with respect to trichloroacetic acid and incubated for 30 min at 4°C. Bovine serum albumin (1 mg) was added as a carrier. The resulting precipitates were separated from the supernatant by centrifugation, and both fractions were assayed for radioactivity.

Viral antigen and concanavalin A (a protein with lectin and immunostimulatory activity) were also assayed for biological activity before and after encapsulation. The virus was assayed by its ability to induce circulating antibody formation after intraperitoneal injection into mice, and the concanavalin A was assayed by its ability to agglutinate rabbit erythrocytes.

RESULTS AND DISCUSSION

Figure 1 illustrates the physical appearance of the microspheres. Preparations made with I lot A were dull white in color, whereas those produced with lot B were shiny white. Other characteristics of both preparations were similar. Most experiments presented in this report, however, were carried out with lot A.

Almost all of the microspheres were hollow, and in the large majority of particles the interior was completely sealed. A cross section of the particles revealed that the encapsulated material was dispersed throughout the I matrix in small pockets (Fig. 2). Fully formed quasi-spherical particles were apparent as early as 1 min after addition of the I solution. As seen from the data in Fig. 3, the size of the particles increased with time, reaching a maximum by 5–10 min after initiation. Coacervation of I, sucrose, and core material appeared to be complete since no I and only trace amounts of radioactivity (probably due to free iodine-125) were detected in the paraffin phase after separation of the microspheres.

It appears that formation of the microspheres occurs by stages. Initially, the finely divided suspension of sucrose/core material in the paraffin oil nonsolvent comes in contact with the I solution. Since the paraffin is also a nonsolvent for I, phase separation of the latter occurs with its deposition around the sucrose microparticles. Coated microparticles then aggregate, rapidly forming small hollow spheres. Further deposition of coated material around the aggregate results in the formation of larger spheres until all the suspended material has been utilized.

The data in Fig. 4 show a linear relationship between the weight of the microspheres and the amount of incorporated ^{125}I-labeled antigen. This indicates that the core material is dispersed uniformly among the particles.

Figures 5–7 summarize the disintegration characteristics of the microspheres under simulated gastric and intestinal conditions. From Fig. 5 it can be seen that, with a I–diethyl phthalate–wax coating, <1% of the encapsulated viral radiolabel was released into the gastric medium in 3 h. By comparison, the I–diethyl phthalate and I coatings were not as effective, releasing ~10 and 17%, respectively. Regardless of the coatings

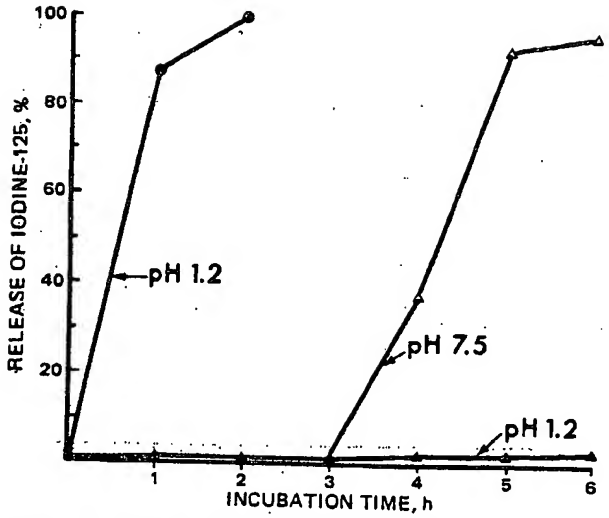

Figure 7—*Influence of pH of the incubation medium on the release of encapsulated concanavalin A at 37°C. Key: (●) uncoated; (▲, △) I–diethyl phthalate–wax coated.*

applied, however, most of the encapsulated protein was released within the first hour of incubation in the intestinal environment. Only 85–90% of the uncoated viral radiolabel (*i.e.*, lyophilized sucrose–viral antigen alone) was released in the first 3 h. The reason for this is not clear, but it may be due to an artifact in the assay system. There are a number of different proteins in the viral antigen preparation with radiolabel attached. Some of these proteins may have been denatured at the low pH of the simulated gastric juice and may have precipitated, in which case they would not have been measured in the supernatants, after centrifugation, as "released" material. Released under intestinal conditions, the same proteins would have remained soluble.

Although the I and I–diethyl phthalate coatings were effective in retaining the high molecular weight material, they had little effect on the retardation of the sucrose efflux, with almost all sucrose being released into the suspending medium within the 3-h test period. In contrast, when a I–diethyl phthalate-wax coating was applied, <20% was released under the same conditions (Fig. 6).

Figure 7 depicts the release of [^{125}I]concanavalin A from I–diethyl phthalate–wax-coated microspheres. Even after 6 h at low pH, there was <5% release, but there was almost complete breakdown at the intestinal pH of 7.5.

The size of the microspheres to some extent determined their release characteristics. In the experiment summarized in Fig. 8, I-coated microspheres prepared with [^{125}I]bovine albumin as the core material were graded through a series of Tyler sieves mounted on a portable sieve shaker[9]. It can be seen that the smaller the diameter, the more rapid the release. Since the size of the microspheres can be controlled to some extent by the time of addition of the chloroform (Fig. 3), the rate of release of their contents can also be controlled.

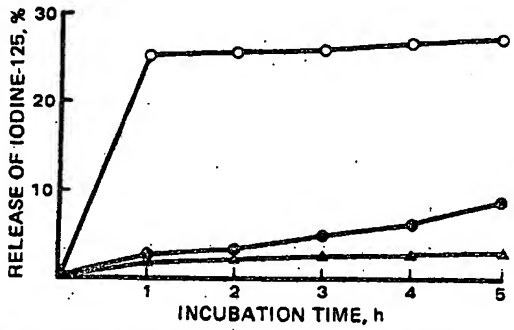

Figure 8—*Influence of size of the microspheres on the release of bovine albumin from simulated gastric juice (without enzymes), pH 1.2, at 37°C. Key: (○) particles retained by a No. 50 sieve; (●) particles retained by a No. 20 sieve; (▲) particles retained by a No. 12 sieve.*

[9] Model RX-24; W. S. Tyler Co. of Canada, Ltd., St. Catherines, Ont.

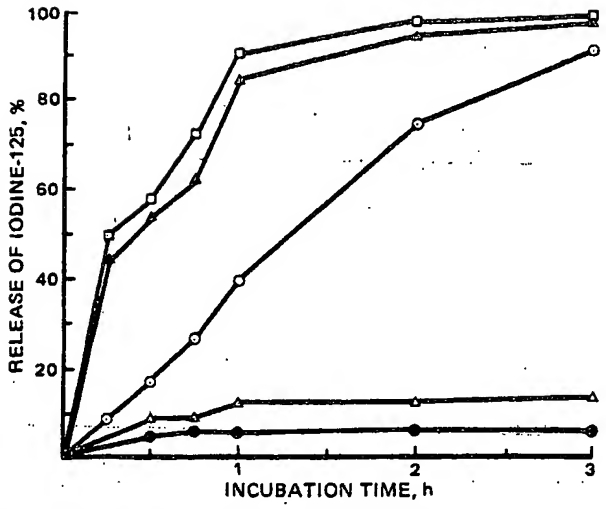

Figure 9—*Effect of pH on the release of viral radiolabel from citrate–phosphate buffer at 37°C. Key: (●) pH 2.5; (△) pH 5.0; (○) pH 6.0; (▲) pH 7.0; (□) pH 8.0.*

The above data indicate that the core materials were effectively released under simulated intestinal conditions. However, the data give no information about the physical state of the labeled material—specifically, whether or not it has been degraded during encapsulation and/or incubation. Studies on trichloroacetic acid-induced precipitation showed that >80% of the viral antigen- and concanavalin A-associated radiolabel was still acid insoluble after 3 h in each of the simulated gastric and intestinal conditions. Additionally, and more importantly, mice injected with the decapsulated viral antigen still produced protective neutralizing antibody titers against rabies virus (indicating that the antigenicity was largely intact), and the decapsulated lectin showed no significant loss of hemagglutinating activity with rabbit erythrocytes.

Figure 9 illustrates the pH dependency of the release of radiolabel from I-diethyl phthalate–wax-coated microspheres with a viral antigen core material. Conditions were the same as in previous experiments except that the buffer system was 0.1 M citrate–phosphate, ranging from pH 2.5 to 8.0. It is clear that the wax coating does not interfere with the release, which is minimal at pH ≤5. Between pH 5 and 7 there is increasingly rapid release, with no significant further increase above pH 7.

CONCLUSIONS

The encapsulation method described here is simple, inexpensive, and rapid; starting with the core material in the form of a finely divided powder, the whole procedure can take <15 min. Furthermore, no specialized equipment is required. The system has similarities to that described by Kitajima and coworkers (11); in their method, however, the core material is suspended in the I solution and the process required 5 h. In the system described here, it was found that if the stirring process was continued for > ~15 min prior to addition of the chloroform, clumping of the microspheres occurred. Since the microspheres were formed considerably before this time, this was no drawback.

In this report, the encapsulation of complex biologicals has been described, but the method can be applied to the encapsulation of many other substances. For example, microspheres have been prepared with such varied materials as cornstarch, tetracycline, saponin, and barium sulfate individually replacing the sucrose. Sucrose microspheres have been prepared containing the following active ingredients (2–60 mg/g of sucrose): scopolamine butylbromide[10], loperamide[11], trifluoperazine–isopropamide[12], and metoclopramide hydrochloride[13]. Encapsulation of cimetidine[14], however, was unsuccessful. The prime requirements appear to be that the materials to be encapsulated are in a finely divided state and that they are insoluble in both the acetone–ethanol and the paraffin phases. The microspheres can also be color-coded by addition of a dye such as malachite green to the I solution, the requirement here being that the dye is insoluble in the paraffin phase.

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ACKNOWLEDGMENTS

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[10] Buscopan; Boehringer Ingelheim (Canada) Ltd., Burlington, Ont.
[11] Imodium; Ortho Pharmaceutical (Canada) Ltd., Don Mills, Ont.
[12] Stelabid Forte; Smith, Kline and French (Canada) Ltd., Mississauga, Ont.
[13] Reglan; A. H. Robins Canada Ltd., Montreal, Que.
[14] Tagamet; Smith, Kline and French (Canada) Ltd., Mississauga, Ont.

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Report

Drug Release from Tablets Containing Cellulose Acetate Phthalate As an Additive or Enteric-Coating Material

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A formulation containing cellulose acetate phthalate for preparing enteric-coated granules was developed with the use of granulation and microencapsulation techniques. Drug release from tablets or tabletted microcapsules was measured in a disintegration apparatus and an *in vitro* variable-pH release simulator of the flow type. The release mechanism for the tablets or tabletted microcapsules was determined with the Higuchi matrix model, a first-order kinetic model, and the Weibull distribution function. Adding acetone directly to the mixture of sulfamethoxazole and cellulose acetate phthalate resulted in enteric-coated granules with more prolonged release than other granulation methods. Microencapsulation of the granules significantly delayed the drug release and enhanced the effectiveness of the enteric coating. Microencapsulated granules show release patterns that are sustained and can be simulated with three different release models, i.e., with square-root time plotting, diffusional first-order plotting, and Weibull distribution plotting. The enteric-coating behavior of the tablets was more clearly demonstrated with the variable-pH release simulator than with a fixed-pH dissolution method.

KEY WORDS: microencapsulation; cellulose acetate phthalate; enteric-coated granules; drug release *in vitro;* sulfamethoxazole.

INTRODUCTION

Cellulose acetate phthalate is a physiologically inert polymer widely used as an enteric-coating material. The pH dependence of cellulose acetate phthalate, which is due to the presence of ionizable phthalate groups, has already been studied (1–3). Many formulations also employ cellulose acetate phthalate in waterproof coats and in enteric coats for tablets, pills, and granules (4,5). We have previously used spray-dried solutions containing the ammonium salts of cellulose acetate phthalate and sulfamethoxazole for the purpose of preparing enteric-coated microcapsules (6); however, interactions between cellulose acetate phthalate and sulfamethoxazole occurred during spray-drying (7). In the present study, a simple procedure was developed with cellulose acetate phthalate for preparing enteric-coated granules. These granules were tabletted in order to compare their release behavior. Furthermore, the granules were microencapsulated with ethylcellulose by a coacervation-phase separation method. Drug release from tablets or tabletted microcapsules was also determined with a disintegration apparatus and an *in vitro* release simulator to evaluate their enteric coation function.

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[3] To whom correspondence should be addressed.

MATERIALS AND METHODS

Preparation of Granules

The formulations for preparing enteric-coated granules are tabulated in Table I, and the preparation methods were as follows.

Method I: Formulation A

Sulfamethoxazole (Shionogi Pharm. Co., Japan) and different sizes of cellulose acetate phthalate powders (CAP; Kishida Chem. Co., Japan) were mixed in a plastic vinyl bag for 7 min by hand shaking, then transferred to a large-volume mortar (Labo-mill, Yamato, Japan) and mixed for 5 min. A 10% (w/v) acacia (Wako Pure Chem. Indus., Japan) solution was slowly added and kneaded for 7 min. The mass was granulated in a wet granulator (Erweka, FRG) and dried in a fluid-bed drier (Glatt, FRG) at 50°C for 30 min.

Method II: Formulation B

Sulfamethoxazole was placed in a large-volume mortar, and a 10% (w/v) CAP–acetone solution was added drop by drop and kneaded until the acetone was nearly evaporated. A 10% (w/v) acacia solution was slowly added, and the mixture kneaded for 7 min and then treated as in method I.

Method III: Formulation C

The granulation procedure of method III was similar to that of methods I and II. Acetone was slowly added before a 10% (w/v) acacia solution was added.

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Table I. Formulations for Preparation of Enteric-Coated Granules

Formulation	Sulfamethoxazole (g)	Cellulose acetate phthalate (g) 60–80 mesh	80–150 mesh	150–200 mesh	>200 mesh	10% acetone solution (ml)	Acetone (ml)	10% acacia solution (ml)
A_1	20	20						40
A_2	20		20					40
A_3	20			20				40
A_4	20				20			40
B_1	40					15		20
B_2	40					30		20
B_3	40					60		20
B_4	40					90		20
C_1	20				20		20	10
C_2	20				20		40	10

All the granules were sieved into suitable fractions with JIS standard sieves. Granule sizes between 32 mesh (500 μm) and 80 mesh (177 μm) were used for tabletting. Mixtures (1:1) of fractioned granules and microcrystalline cellulose (Avicel-101, Asahi Kasei Kogyo K.K., Japan) were tabletted in a single-punch tablet machine (Erweka, FRG).

Preparation of Microcapsules

Granules (5 g), ethylcellulose (3 g; Ethocel 100 cps; ethoxy content, 49.5%; Dow Chemical Co., USA), and cyclohexane solution (300 ml) were used for microencapsulation. The microcapsules were prepared by a phase separation method similar to that previously described (8–10). The microcapsules were mixed with microcrystalline cellulose (1:1) and tabletted with a single-punch tablet machine.

Dissolution Studies of Tablets

The dissolution test of a tablet was undertaken using the JP IX disintegration apparatus and test solution (pH 1.2 and pH 7.5) at 37°C. Tests were also conducted with an *in vitro* release simulator with a flow-type dissolution container in which the pH of the medium was continuously changed to simulate the pH change on the surface of the tablets in the GI tract. The apparatus and dissolution method were previously described (6). Sulfamethoxazole in the medium was determined spectrophotometrically (pH 1.2, 267 nm; pH 7.5, 258 nm) with a double-beam spectrophotometer (Model 556, Hitachi, Japan).

Dissolution Data Analysis

The release mechanisms of drugs from matrix was analyzed via three different models.

Higuchi Matrix Model

Drug diffusibility from the matrix is the rate-determining factor in the release mechanism (11) according to Eq. (1).

$$Q = [D(2A - C_s)C_s t]^{1/2} \quad (1)$$

where Q is the amount of drug released per unit area at time t, D is the drug's apparent diffusion coefficient in the matrix, A is the total drug content, and C_s is the drug solubility. Equation (2), describing drug release from the microcapsules or pellets, can be derived from Eq. (1) (12).

$$C_r = 100 \cdot S_v(2DC_s t/A)^{1/2} \quad (2)$$

where C_r is the percentage of drug released and S_v is the specific surface area. This equation describes drug release (%) as a function of the square root of time and can be simplified:

$$C_r = K_h t^{1/2} \quad (3)$$

$$K_h = \text{slope} = 100 \cdot S_v(2DC_s/A)^{1/2} \quad (4)$$

where K_h is the slope of the linear plot and represents the release rate constant.

First-Order Kinetics

The classical first-order equation was used for evaluation of a membrane-controlled mechanism of the encapsulated drug. The diffusion law can be expressed as follows (13):

$$\log W = \log W_o - \frac{K_f t}{2.303} \quad (5)$$

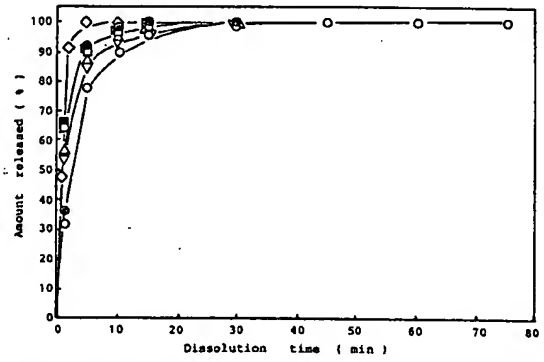

Fig. 1. Release of sulfamethoxazole from tablets prepared from Formulation A. (◇) Sulfamethoxazole powder; (△) Formulation A_1; (□, ■) Formulation A_2; (▽) Formulation A_3; (○, ●) Formulation A_4. Open symbols, in pH 1.2; filled symbols, in pH 7.5.

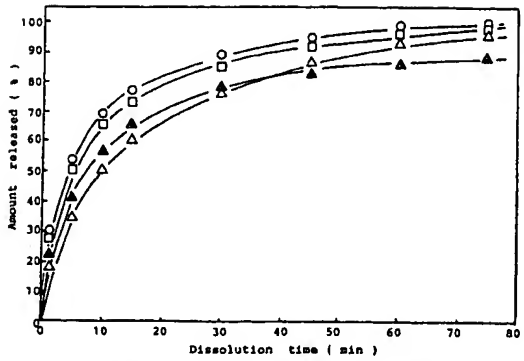

Fig. 2. Release of sulfamethoxazole from tablets prepared from Formulation B in pH 1.2 solution. (○) Formulation B_1; (□) Formulation B_2; (△) Formulation B_3; (▲) Formulation B_4.

where W_o is the initial quantity of drug in the matrix, W is the quantity of drug remaining in the matrix, and K_f is a first-order release constant.

Weibull Distribution Function

Since the tablets quickly disintegrated into small granules after which dissolution started, the Weibull distribution was used to fit the dissolution curves (14).

$$\log[-\ln(W/W_o)] = b \log(t - T_i) - \log a \quad (6)$$

$$a = (T_d)^b \quad (7)$$

where a is a scale parameter and b is a shape parameter. T_i is a location parameter, and T_d represents the time interval necessary to dissolve 63.2% of the drug.

RESULTS AND DISCUSSION

Dissolution Behavior of Tablets in the Disintegration Apparatus

Drug release from the tablets prepared with CAP as an additive (Formulation A) in the disintegration test solutions was determined with a disintegration apparatus (Fig. 1). The tablets disintegrated immediately in both pH 1.2 and pH 7.5 solutions, leading to a fast dissolution rate of the drug. Therefore, CAP in this formulation did not show any enteric-coating property. When CAP–acetone solution was directly added to the sulfamethoxazole particles (Formulation B), the dissolution rate of these tablets was slower than that of Formulation A tablets (Fig. 2). The larger the amount of CAP–acetone solution, the more delayed the dissolution rate. Possibly CAP is coated onto the sulfamethoxazole particles, forming an enteric-coating film with a resulting slower dissolution rate. However, in the initial 40 min of dissolution, tablets prepared with 90 ml of CAP–acetone solution resulted in a higher dissolution rate than tablets prepared with 60 ml of CAP–acetone solution. Scanning electron microscopy suggested that sulfamethoxazole dissolves in acetone and salts out to some degree on the surface of the CAP agglomerates during drying. Formulation C, in which ace-

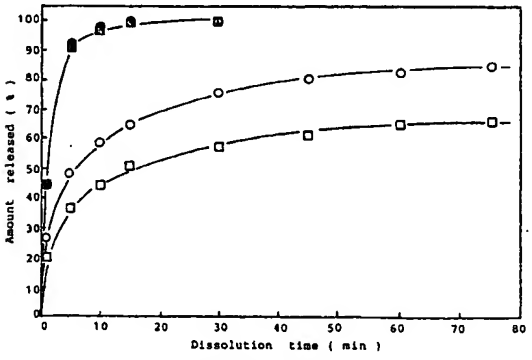

Fig. 3. Release of sulfamethoxazole from tablets prepared from Formulation C. (○, ●) Formulation C_1; (□, ▣) Formulation C_2. Open symbols, in pH 1.2; filled symbols, in pH 7.5.

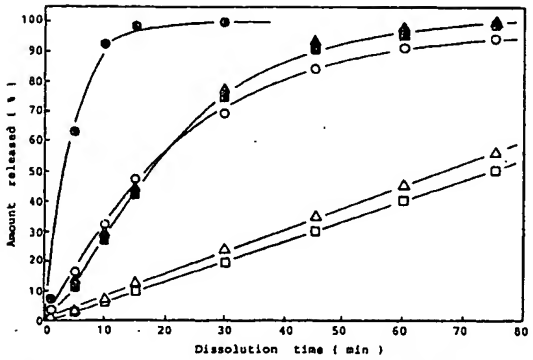

Fig. 4. Release of sulfamethoxazole from tabletted microcapsules prepared from different formulations. (○, ●) Formulation A_3 MC; (△, ▲) Formulation B_1 MC; (□, ■) Formulation B_4 MC. Open symbols, in pH 1.2; filled symbols, in pH 7.5. MC, microcapsules.

Table II. Evaluation of the Release Mechanism of Sulfamethoxazole Release from Different Types of Tablets

Formulation	Release mechanism: First-order kinetic (r^2)[a]	Higuchi matrix model (r^2)	Weibull function (r^2)
A_1	− (0.9884)	− (0.9637)	− (0.9889)
A_2	− (0.9898)	− (0.9736)	− (0.9638)
A_3	− (0.9840)	− (0.9825)	− (0.9763)
A_4	− (0.9825)	− (0.9845)	− (0.9504)
B_1	− (0.9813)	+ (0.9983)	− (0.9794)
B_2	− (0.9846)	+ (0.9973)	− (0.9877)
B_3	− (0.9837)	+ (0.9989)	− (0.9761)
B_4	− (0.9763)	+ (0.9979)	− (0.9894)
C_1	− (0.9874)	− (0.9837)	+ (0.9950)
C_2	− (0.9843)	− (0.9869)	+ (0.9941)
A_3 MC[b]	+ (0.9996)	+ (0.9954)	+ (0.9978)
B_1 MC	+ (0.9957)	+ (0.9995)	+ (0.9953)
B_4 MC	+ (0.9967)	+ (0.9987)	+ (0.9992)

[a] Linear regression coefficient of slope.
[b] Microcapsule.

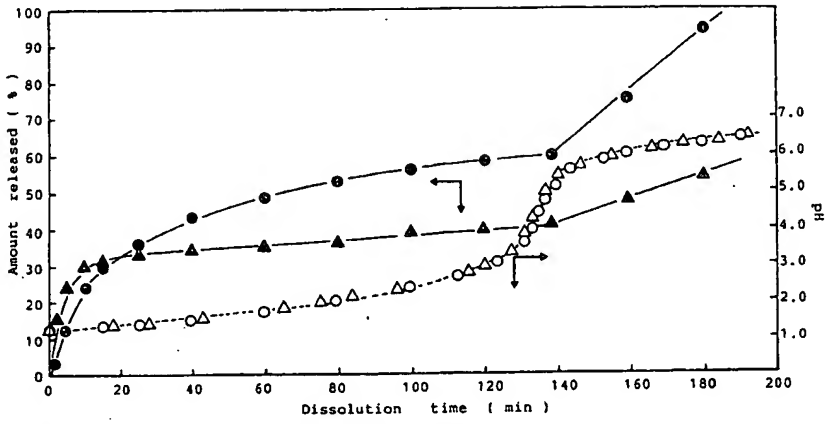

Fig. 5. Drug release (filled symbols) and pH change (open symbols) patterns in a flow-type simulator for tablets prepared from Formulation C. (○, ●) Formulation C_1; (△, ▲) Formulation C_2.

tone was directly added to the mixtures of sulfamethoxazole and CAP, produced the dissolution curve shown in Fig. 3. Drug release from these tablets was significantly slower at pH 1.2 than at pH 7.5. The effectiveness of the enteric-coating of Formulation C was greater than that of other formulations. Furthermore, the larger the amount of acetone used, the slower the dissolution behavior.

Drug released from the tabletted microcapsules is shown in Fig. 4. The dissolution curves in the pH 7.5 solution were distinguished by their much faster release rate from those in the pH 1.2 solution, and the prolonged-release behavior of tabletted microcapsules in the acidic solution was pronounced, showing again the effectiveness of the enteric coating of the microencapsulated granules. This result might have been due to the fact that the microencapsulated granules were compressed, forming a CAP–ethylcellulose matrix-like pellet that resulted in the prolongation of drug.

The release mechanism of tablets prepared with different granulation methods and microencapsulation technique was examined. Three different models of the release mechanism were tested with Eqs. (1) to (7). The linearity of slope was evaluated by estimating their linear regression coefficients (Table II). Drug release from Formulation A does not conform with any of the release mechanisms because of rapid disintegration and dissolution. Formulations B and C fit the Higuchi matrix model and Weibull function, respectively. However, the release from tabletted microcapsules fit the three different release mechanisms equally well. This suggests that the microencapsulated granules belonged to the prolonged-release matrix-type pellets.

Dissolution Behavior of Tablets in a Flow-Type Simulator

As an orally administered drug preparation moves from the stomach (pH 1–3) through the pylorus to the duodenum (pH 5–7), its pH environment continuously changes. The upper small intestine is likely to be slightly acidic. Thus, to simulate the *in vivo* pH environment, it was desirable to conduct the enteric test in a dissolution medium whose pH continuously changes from 1.2 to 7.0 rather than in a me-

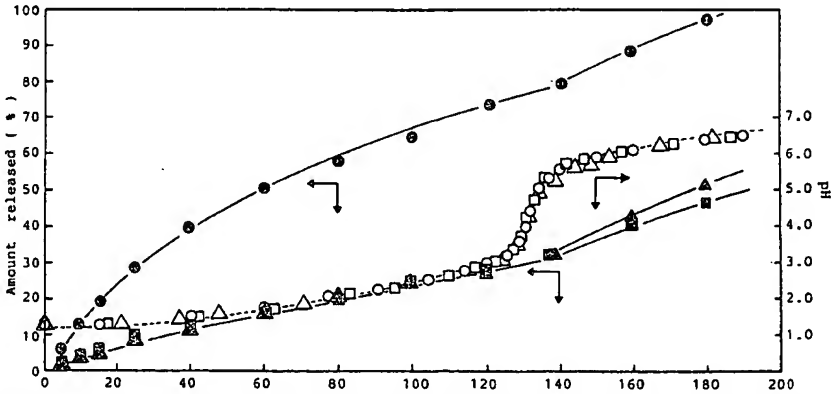

Fig. 6. Drug release (filled symbols) and pH change (open symbols) patterns in a flow-type simulator for tabletted microcapsules prepared from different formulations. (○, ●) Formulation A_3 MC; (△, ▲) Formulation B_1 MC; (□, ■) Formulation B_4 MC. MC, microcapsules.

dium with a fixed pH. Release patterns of tablets prepared from the mixtures of microcrystalline cellulose and the different granules with or without microencapsulation were examined with an *in vitro* release simulator (Figs. 5 and 6). The pH change of the medium from 1.2 to 7.0 with dissolution time followed a sigmoidal curve, with only small changes between experiments. The drug release from tablets prepared from Formulation C was relatively fast over 20 min, followed by a constant release rate (Fig. 5). After the dissolution time of 140 min at pH 5.0–5.5, the release rate increased rapidly again, which caused an inflection on the release curves. It is reasonable to assume that this inflection point corresponds to the starting point of the enteric action. This result agreed with release profiles of the enteric-coated microcapsules prepared by the spray-drying technique (6). Moreover, the present study also confirms that CAP dissolves at approximately pH 5.4 (15). The release pattern of the tabletted microcapsules did not clearly indicate the inflection point on the release curves, but after pH 5.4 was reached the dissolution rate tended to increase (Fig. 6). The present study suggests that the enteric-coating activity of the tablets was more clearly demonstrated with the flow-type variable-pH release simulator than by studying dissolution at a constant pH value.

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Enteric-Coated Aspirin Bezoar: Elevation of Serum Salicylate Level by Barium Study

Case Report and Review of Medical Management

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The gastric accumulation of enteric-coated aspirin tablets due to peptic ulcer disease or gastric outlet scarring and the impaired gastric emptying that results have been previously reported. In the case reported herein, an unanticipated peaking of plasma salicylate levels occurred following radiographic studies in which barium was used. This phenomenon prompted an in vitro study in which dissolution rates of enteric-coated aspirin in various barium preparations were determined, suggesting that dissolution is dependent upon effervescent activity of the milieu, as well as pH. The use of barium in diagnosing suspected accumulation of enteric-coated aspirin is discussed, and techniques for tablet removal are reviewed.

Because of its ability to provide greater gastrointestinal safety than regular aspirin, enteric-coated aspirin has a long history of use in situations in which long-term aspirin administration is necessary. This advantage results from the tablet's surface layer of cellulose acetate phthalate, a component that is stable until environmental pH exceeds 6.0 to 6.8, usually achieved only distal to the pylorus.

Since 1973, seven cases of accumulated enteric-coated aspirin have appeared in the English literature; all these cases reported gastric outlet obstruction, a clinical situation that could allow these tablets to remain intact for extended periods in an acid milieu. Baum [1] recently summarized the clinical aspects of six of these reports, including the various management approaches.

Prompted by our experience with an eighth patient in whom we observed a curious correlation between a barium radiographic study and a rise in serum salicylate level, we report on the results of an in vitro study of enteric-coated aspirin dissolution in barium, as well as successful medical management using a sodium-bicarbonate ($Na\text{-}HCO_3$) lavage technique first described by Sogge et al [2].

CASE REPORT

A 77-year-old woman with a 17-year history of classic rheumatoid arthritis was admitted for evaluation of anorexia, early satiety, nausea, weight loss, and vomiting of most solid foods over the previous three weeks. She had no prior history of acid peptic disease and denied symptoms of gastrointestinal blood loss.

Management of her rheumatoid arthritis had consisted solely of salicylates or nonsteroidal anti-inflammatory agents. Because of epigastric distress several weeks previously, her treatment had been changed from regular aspirin (12 to 18 tablets daily) to a similar schedule of enteric-coated aspirin tablets; in addition, empiric treatment with ranitidine and antacids was started. While taking the enteric-coated aspirin, she noted

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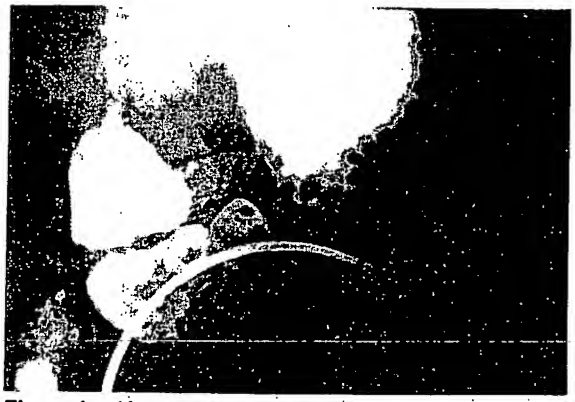

Figure 1. Upper gastrointestinal contrast series demonstrating multiple rounded luminal defects produced by undissolved enteric-coated aspirin tablets.

increasing joint pain and immobility. She denied confusion, tinnitus, or other symptoms of salicylism.

Examination revealed an alert, cachectic woman with advanced typical rheumatoid deformities of the upper and lower extremities and signs of active synovitis. The abdomen was scaphoid and nontender. Testing for stool occult blood was trace positive.

The salicylate level after admission was less than 3.0 mg/dl. An upper gastrointestinal contrast radiographic series with barium revealed a large antral ulcer, subtotal gastric outlet obstruction, and multiple rounded luminal filling defects consistent with retained undissolved tablets (**Figure 1**). Following the barium study, the salicylate level was 31.4 mg/dl. Gastric saline lavage via an Ewald tube was unsuccessful at removing the tablets. Subsequently, 1.5 liters of isotonic $NaHCO_3$ was used to lavage the stomach in a push-pull fashion for 90 minutes, until the fluid was clear; approximately 35 enteric-coated aspirin tablets were recovered. The salicylate levels over the next four days were 28 mg/dl, 22 mg/dl, 15 mg/dl, and 5 mg/dl sequentially. However, on the fourth day, the patient vomited contents containing a completely intact enteric-coated tablet. Endoscopic evaluation then revealed 15 to 20 remaining tablets in addition to the prepyloric ulcer crater. Over the next 24 hours, 7.2 liters of $NaHCO_3$ solution (150 meq/liter) were infused via a nasogastric tube at a rate of 300 ml/30 minutes, alternating with 30 minutes of continuous suction, as per the recommendations of Sogge and colleagues [2]. A pH of 10 was achieved in the gastric milieu of the stomach; salicylate levels during this period were 21 mg/dl or less. This procedure was well tolerated with minimal discomfort and no symptoms of salicylism. Repeat endoscopy demonstrated that all tablets and debris had been removed and that no esophageal or gastric complications resulted from the lavage procedure. The patient was discharged following a period of total parenteral nutrition.

MATERIALS AND METHODS

In each of six flasks, 10 enteric-coated aspirin tablets were added to 100-ml solutions of various pH: hydrochloric acid at pH 3 and 5; water at pH 7; and full-strength and half-strength barium sulfate solutions (E-Z-EM, Westbury, New York; e z hd Barium Sulfate for Suspension: [label] 98 percent barium sulfate plus sorbitol, dispersing agent, simethicone, natural and artificial flavors, artificial sweetener, and color; [specific ingredients] 98.6 to 99.3 percent barium sulfate, 0.3 to 0.9 percent sorbitol, 0.08 to 0.12 percent simethicone, 0.02 to 0.07 percent wetting agent, and less than 0.01 percent NaCitrate, polyoxyethyleneglyceryl, and other ingredients); and $NaHCO_3$ solution at pH 9. The flasks were kept at 25°C, gently stirred intermittently, and observed over a 72-hour period (**Table I**).

The barium whole product (E-Z-EM) was then separated into its respective components (courtesy of E-Z-EM for our experiments): barium sulfate, gums, and flavors and colorings, and into these solutions tablets were added. Separate samples were observed, both with and without continuous gentle agitation, over a 72-hour period (**Table II**). In addition, various admixtures of these components were tested for their ability to dissolve enteric-coated aspirin tablets (**Table III**).

A second brand of commercial barium sulfate solution was also tested (Mallinckrodt, St. Louis, Missouri; Barosperse barium sulfate for suspension USP: [label] 95 percent barium sulfate USP, plus artificial color, flavorings, sweetener, and additional ingredients that enhance suspending and fluidizing characteristics) (Table II).

Finally, because effervescent granules are often administered with barium solutions to provide air-contrast upper gastrointestinal studies, such granules (Mallinckrodt; Upjohn) were added to the two commercial barium prepara-

TABLE I Dissolution of Enteric-Coated Aspirin Tablets in Solutions of Varying pH

Contents (100 ml)	HCl	HCl	H_2O	$BaSO_4$ (E-Z-EM) Full Strength	$BaSO_4$ (E-Z-EM) Half Strength	$NaHCO_3$
Number of tablets dissolved (of 10)	0	0	0	4	0	10
Initial pH	3	5	7	7	7	9
Final pH	3	5	7	4.6	7	6.5

HCl = hydrochloric acid; H_2O = water; $BaSO_4$ = barium sulfate; $NaHCO_3$ = sodium bicarbonate.

TABLE II Dissolution of Enteric-Coated Aspirin Tablets by Separate Components of a Commercial Barium Preparation (E-Z-EM) and by a Second Brand (Mallinckrodt)

Contents (100 ml)	$BaSO_4$ (E-Z-EM)		Gums		Flavorings and Colorings		$BaSO_4$ (Mallinckrodt)	
	A	S	A	S	A	S	A	S
Number of tablets dissolved (of 10)	0	0	0	0	0	0	0	0
Initial pH	5	5	6	6	7	7	7	7
Final pH	5	5	6	6	7	7	7	7

$BaSO_4$ = barium sulfate; A = agitate; S = still.

tions and were likewise observed for their ability to dissolve enteric-coated aspirin tablets (Mallinckrodt's Baros Effervescent Granules [label] per single dose: 1.38 g $NaHCO_3$, 1.26 g tartaric acid, and 0.036 g simethicone [will produce 320 ml of carbon dioxide with water]; Upjohn's CitroCarbonate [label] composed per teaspoonful of 2.34 g $NaHCO_3$, 1.19 g citric acid anhydrous, 254 mg NaCitrate hydrous, 151 mg CaLactate pentahydrate, 79 mg sodium chloride, 44 mg monobasic sodium phosphorous anhydrous, and 42 mg magnesium sulfate dried).

RESULTS

The enteric-coated aspirin tablets remained intact in all flasks except in those containing the full-strength E-Z-EM barium, the $NaHCO_3$ and the preparations with the effervescent granules (Tables I through IV). In the E-Z-EM barium solution, five (average of three runs) of the 10 tablets dissolved within four to seven hours; however, no additional tablets dissolved after that time (Figure 2). During that same time period, pH was noted to decrease from 7 to 4.6. All tablets in the $NaHCO_3$ solution and in both the barium solutions containing the effervescent granules dissolved within two hours. The second brand of barium (Mallinckrodt) did not by itself dissolve the tablets.

COMMENTS

The association between retained enteric-coated aspirin tablets, peptic ulcer disease, and gastric outlet obstruction has been reported previously [2–8]. In common with the seven previous reports of enteric-coated aspirin retention, our patient experienced anorexia, weight loss, vomiting, early satiety, and epigastric discomfort, but escaped the symptoms of salicylate toxicity found in four of these cases [3–6]. During the workup of such symptomatic patients, barium ingestion studies are often undertaken, which may result in the abrupt dissolution of the enteric-coated aspirin tablets and subsequent rapid increases in serum salicylate levels.

The stability of the cellulose acetate phthalate coating was shown by Halla et al [3] in an in vitro study to exceed Food and Drug Administration requirements of acid resistance for at least four hours; each of the previous case reports has suggested the presence of undissolved, re-

TABLE III Dissolution of Enteric-Coated Aspirin Tablets in Various Admixtures of Components of Commercial Barium Preparation (E-Z-EM)

Mixtures (100 ml)	Number of Tablets Dissolved (of 10 tablets)
$BaSO_4$ plus flavors and colors	0
$BaSO_4$ plus gums	0
Gums plus flavors and colors	0

$BaSO_4$ = barium sulfate.

TABLE IV Dissolution of Enteric-Coated Aspirin Tablets in Barium Preparations after Addition of Effervescent Granules

Contents	$BaSO_4$ (E-Z-EM)	$BaSO_4$ (E-Z-EM) plus Citro-Carbonate Granules	$BaSO_4$ (Mallinckrodt)	$BaSO_4$ (Mallinckrodt) and Granules
Number of tablets dissolved (of 10)	6	10	0	10
Time of dissolution (hours)	6	2	—	1.5

$BaSO_4$ = barium sulfate.

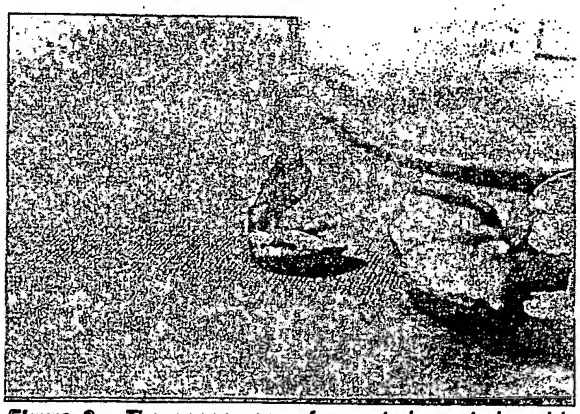

Figure 2. The appearance of an enteric-coated aspirin tablet after in vitro dissolution by barium sulfate suspension.

tained tablets for at least several days [2–8]. In light of this stability, several mechanisms have been proposed to explain measurable salicylate levels and even toxicity in the face of outlet obstruction. These include flaws in the coating of some tablets, elevation of gastric pH by intercurrent use of oral antacids [7], and passage of some or all tablets into the intestine, either spontaneously or as a result of repeated abdominal palpation [6]. In the latter case, as reported by Springer and Groll [6], the patient also experienced salicylate toxicity and disappearance of the tablets within 72 hours of a barium ingestion study. Since there was no known interaction between barium sulfate and the polymer coating of the enteric-coated aspirin tablets, these investigators suspected that tablet disintegration was largely secondary to repeated palpation. In the case reported by Sherry [8], melena and hematemesis developed in the patient after a barium study [8]. And in the most recent case report, frank acute salicylate toxicity developed after barium ingestion [5]. Our patient, though asymptomatic, also demonstrated a curious rise in the serum salicylate level, from essentially zero to 31.4 mg/dl after barium ingestion.

Although the exact mechanism of this dissolution remains unclear, our experiments seem to support certain conclusions. First, some commercial barium preparations may lyse enteric-coated aspirin tablets at pH 7, whereas other products, at pH 7, like water, do not. No tablets dissolved in a pH of less than 4, and all dissolved in a pH of 9. This suggests that although pH plays an important role in this interaction, it is not the sole factor. Second, although defects in the coating of some tablets may be a factor, agitation (and hence possible abrasion) did not influence the lysis of enteric-coated aspirin tablets. However, such defects might explain why some tablets in the barium preparation were lysed while others were not. Third, the addition of effervescent material clearly had a positive influence on enteric-coated aspirin dissolution, and the barium preparations alone may have some effervescent action because of other additives. The influence of such effervescence may explain why oral antacids alone, although raising gastric pH, may not lead to dissolution of enteric-coated aspirin tablets, and thus to salicylism, in unrecognized enteric-coated aspirin bezoars [3,5,8]. Since all our experiments were performed at 25°C, the influence of body temperature has not been evaluated. No attempt was made to demonstrate statistically significant differences in the dissolution of tablets, and we encourage others to verify these findings on a larger scale.

Whatever the mechanism of interaction, prompt evacuation of retained enteric-coated aspirin tablets should be initiated when they are recognized on a barium study. Various treatment approaches have included gastrotomy, induced emesis, palpation, Ewald tube lavage [9], and the method of gastric lavage with isotonic $NaHCO_3$ described by Sogge et al [2]. We found the last method to be both successful and safe and recommend it as the method of choice for the resolution of enteric-coated aspirin bezoars. However, if gastric outlet obstruction is suspected in a patient consuming enteric-coated aspirin tablets, endoscopy may be the diagnostic method of choice, so that the potential abrupt dissolution of the tablets by barium products and/or the effervescent granules used in barium studies is avoided. Repeat endoscopy to ensure evacuation of tablets after $NaHCO_3$ lavage seems appropriate.

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Reviews

Enteric coated naproxen tablets

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Key words: Naproxen - Enteric coated tablets - Bioavailability - Gastro-intestinal transit.

Summary

It is postulated that the gastroduodenal mucosal side effects of naproxen are partly based on topical toxicity. With enteric coated aspirin tablets as a model product, enteric coated naproxen formulations have been developed. The extent of absorption is the same for enteric coated and plain tablets. The onset of absorption is delayed as a result of retention of larger particles in the stomach and more so when taken along with food. The gastric emptying of enteric coated naproxen granules is less influenced by food intake, but so far without any verified reduction of gastroscopic findings. The gastro-intestinal transit has been studied by use of gamma scintigraphy.

Introduction

The aim of new drug delivery systems like controlled release, delayed release and drug targeting systems is either to boost or delay the absorption rate in order to improve the effect (compliance) or to reduce side-effects. Numerous controlled release formulations based on various technologies have been introduced during the last decades for a variety of drugs, whereas site-specific drug delivery systems are still in an experimental stage for conventional drugs.

Naproxen, being a weak acid (pKa= 4.15), is readily absorbed from both oral and rectal formulations. Use of the more solubile sodium salt, however, enhances the rate of absorption both rectally[1] and orally[2]. The oral administration of the drug is far the most common route although it may cause dyspepsia and upper gastro-intestinal side effects, as is the case for NSAID generally. It is believed that both a topical and a systemic effect of the drug are involved. A possible way to reduce the topical gastroduodenal mucosal damage is to develop an enteric-coated drug delivery system which in most cases will pass through the stomach unchallenged and later on dissolve in the small intestine. Anti-inflammatory doses of aspirin are likely to produce gastroduodenal damage with microbleeding and ulcerations. With enteric-coated drug delivery systems the damage of aspirin is significantly reduced[3,4].

Although naproxen is a drug with reported lower incidence of gastro-intestinal side effects than aspirin[5], a reduction of the gastro mucosal toxicity with an enteric coated drug delivery system is expected. Theoretically a rectal delivery system may reduce the gastro intestinal side effect but will on the other hand introduce other forms of local discomfort. Sodium naproxen suppositories are more likely to give local irritation and microbleeding than naproxen (unpublished data).

Co-administration of mucosal protecting agents like prostaglandins and anti-ulcerative drugs may reduce the incidence of mucosal bleeding, but on the other hand will introduce new problems for the patients.

Bioavailability

The absorption of enteric coated tablets, (Nycopren^{R}), has been studied in healthy volunteers both after intake of a single dose and in steady state conditions[6].

Fig. 1 and Fig 2 show the mean naproxen plasma concentration after a single and repeated dose (500 mg) respectively.

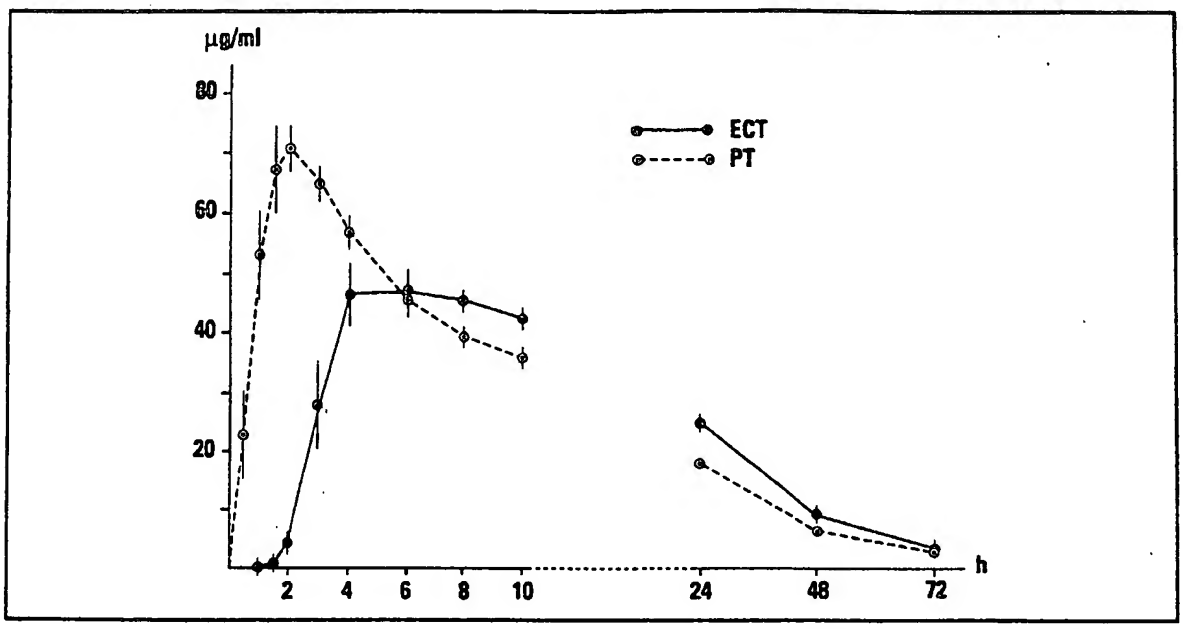

Figure 1. Mean naproxen plasma concentrations ± SEM after oral administration of enteric coated (ECT) and plain naproxen tablets (PT) under fasted conditions, given in equivalent, single doses (500mg). (Gamst et al. 1984).

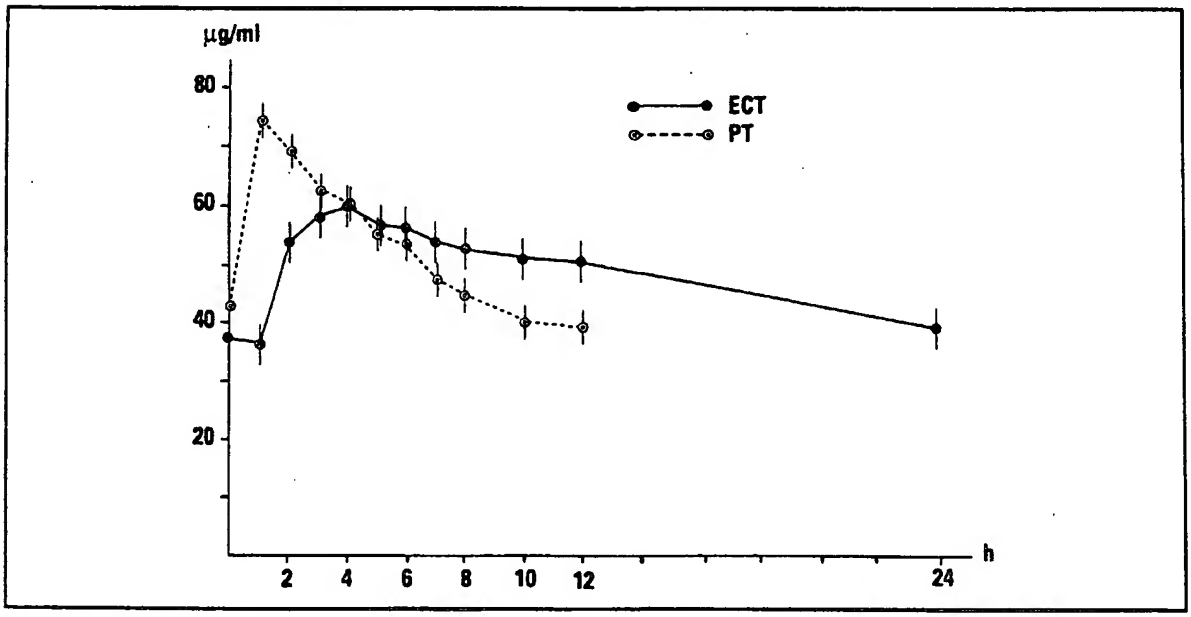

Figure 2. Mean naproxen plasma concentrates ± SEM in steady state after repeated oral administration of enteric coated naproxen tablets (ECT), given once daily, and plain naproxen tablets (PT), given twice daily in equvivalent daily doses (500mg). (Gamst et at. 1984).

The principal factors to influence the absorption of enteric coated naproxen tablets are: the gastric residence time, the intestinal pH and to some extent the characteristics of the tablet in particular the coating layer. A delay in gastric emptying of the tablets is likely to occur with the presence of food.

Large tablets will remain in the stomach until all the food is digested, whereas smaller tablets (≤ 7 mm) may be transferred to the small intestine in some cases together with the food[7] during the fed phase.

The result of this transfer pattern is a typical lag-time on the absorption curve (Fig. 1-3). Thus the rate of absorption from enteric coated tablets is delayed compared with plain tablets, resulting in a significantly higher plasma concentration 10-12 hours after dosing.

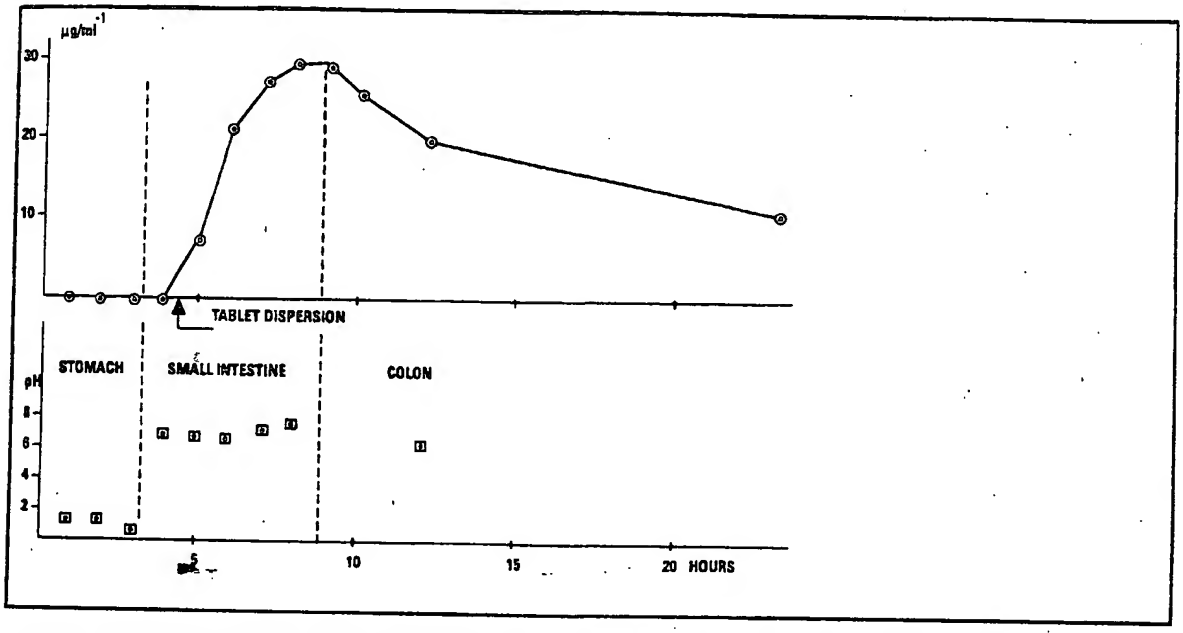

Figure 3. Recorded pH values, median naproxen plasma concentration and time for tablet dispersion assessed by gamma scintigraphy after postprandial intake of 250 mg enteric coated naproxen tablets (n=6) labelled with indium-111. The pH-capsules were labelled with technetium 99m. (Hardy et al. 1987).

Patients taking the tablet in the evening might benefit from a high morning plasma concentration the next day. The extent of absorption is comparable for enteric coated and plain tablets[6].

Gastrointestinal transit

The gastrointestinal transit of enteric coated naproxen tablets radiolabelled with indium-111 have been monitored in vivo by gamma scintigraphy[8] in healthy volunteers. In this particular study the tablets were given postprandially along with a pH sensitive capsule radiolabelled with technetium 99m. The indium and technetium images were obtained simultaneously, but recorded by computer for subsequent analysis. Fig. 3 shows the absorption curve (median values) after consumption of 250 mg naproxen enteric coated tablets and the pH values recorded. There was a close (r= 0.968) correlation between tablet dispersion as observed by gamma scintigraphy and the initial detection of naproxen in the plasma. The gastric residence time is very much influenced by concomitant intake of food and probably also by the size of the tablets. Large particles will normally remain in the stomach during the fed phase. In the interdigestive period which is characterized by a cycle of motility known as the migrating motor complex (MMC) indigestible solids will be emptied eventually during phase 3, the so-called "housekeeper wave".

The intestinal transit time, however, is not influenced by food intake and similar findings are reported for different drug delivery systems like solutions, pellets and single units[9].

In healthy individuals the intestinal transit time is about 3-4 hours. For enteric coated naproxen tablets an average intestinal transit time of 3.6 hours has been recorded with disintegration taking place on average 1.2 hours after leaving the stomach. It is assumed that a delayed dispersion of the tablets after entering the small intestine, may prevent gastric erosion due to reflux of disintegrated tablets back into the stomach[10].

Based on data available from the gamma scintigraphy study, it can be concluded that the small

intestine is the main absorption area for the enteric coated naproxen tablets.

The gastric emptying of multiparticle systems like enteric coated granules are normally less influenced by food intake than single unit products[9]. However, with enteric coated naproxen granules administered in gelatine capsules, the gastric emptying was significantly delayed by dosing after a meal[11]. Furthermore, Aabakken et al (this journal) have failed to show any reduction of the gastroduodenal lesions from enteric coated granules compared to plain tablets.

Enteric coated tablets, either given fasted or after a light meal, might be a favourable dosage form for the administration of naproxen. It should, however, be ruled out that the patient suffers from pyloric stenosis which may cause gastric outlet obstruction.

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